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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/125,022	11/24/1998	SILVIO DE FLORA	P8903-8035	7341

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ARENT FOX KINTNER & KAHN
1050 CONNECTICUT AVENUE, N.W.
SUITE 600
WASHINGTON, DC 20036-5339

EXAMINER	
OWENS JR, HOWARD V	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/125,022	Applicant(s) DE FLORA ET AL.	
	Examiner Howard V Owens	Art Unit 1623	

-- The MAILING DATE of this communicati n appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(a) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/25/01 has been entered.

The text of those sections of Title 35, U.S. Code 103 not included in this action can be found in a prior Office action.

35 U.S.C. 103(a)

Claims 13 - 15 are rejected under 35 U.S.C. 103 as being unpatentable over Freeman et al., *Toxicology and Applied Pharmacology*, vol. 54, pp. 168-175 in combination with Doroshow et al., *J. Clinical Investigation*, vol. 68, pp. 1053 - 64, for the reasons already of record on pages 2 - 4 of the Office action mailed 2-25-99.

The claims are directed to a method for inhibiting cancer metastasis formation in a host comprising the administration of a synergistically effective amount of N-acetyl-cysteine and doxorubicin. Claim 14 specifies that the dosage of N-acetylcysteine be

between 100 mg and 6g/day. Claim 15 requires that the doxorubicin be administered in an amount of between 2 and 10 mg per dose.

Freeman et al. anticipates the combination of doxorubicin and N-acetylcysteine in the treatment of cancer in the dosage ranges that overlap with applicant's ranges (see table 1). Moreover, the improved chemotherapeutic efficacy or synergism of doxorubicin when combined with N-acetylcysteine is taught by Freeman et al. as it teaches (p.174, col.1-2), *"In fact, at the lower dose or adriamycin, the increase in life span was even greater with concurrent administration of the sulfhydryl compounds, which suggests that the adriamycin-sulfhydryl compound combination potentiates the antineoplastic effect of adriamycin"*. Freeman et al. does not specifically target metastasis and applicant has argued in the response filed 11-24-01 that since the instant claims are drawn to inhibiting cancer metastasis, the claims are not anticipated by the prior art of record which applicant asserts that the references only teach the treatment of solid tumors and not metastasis.

Applicant's attention should be drawn to Doroshow et al. wherein it is taught (introduction, paragraph I) that "doxorubicin is an antineoplastic antibiotic that is now part of standard chemotherapeutic regimens for most hematopoietic malignancies as well as for advanced solid tumors of the breast, ovary, thyroid and bone" which adequately bridges the nexus between the differences in the prior art and the invention as claimed.

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to combine N-acetylcysteine with doxorubicin.

The examiner maintains the position that a person of ordinary skill in the art would have been motivated to combine N-acetylcysteine with doxorubicin in a synergistic composition given the art recognized benefits of improved chemotherapeutic efficacy in the combination of sulfhydryl containing compounds such as N-acetylcysteine with doxorubicin (adriamycin). Note, in order to support a basis of obviousness, absolute certainty is not required, one of ordinary skill in the art need only be provided with a reasonable expectation of success and the examiner maintains the

position that along with the art recognized synergistic effects of combining doxorubicin with N-acetylcysteine, one of ordinary skill in the art would be provided with a reasonable expectation of success that an antimalignant agent would be useful in the treatment of metastasis given that ; thus, applicant's arguments are not convincing and the rejection of record is maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Howard Owens whose telephone number is (703) 306-4538 . The examiner can normally be reached on Mon.-Fri. from 8:30 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Primary Examiner signing this action, Gary Geist can be reached on (703) 308-4624 . The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Howard Owens
Group 1623

JAMES O. WILSON
PRIMARY EXAMINER
GROUP 1600